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Published in:
Acta Obstetricia et Gynecologica Scandinavica

DOI:
[10.1111/aogs.13139](https://doi.org/10.1111/aogs.13139)

Publication date:
2017

Document version
Publisher's PDF, also known as Version of record

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Citation for published version (APA):
Volgsten, H., & Schmidt, L. (2017). Live birth outcome, spontaneous pregnancy and adoption up to five years after undergoing assisted reproductive technology treatment. *Acta Obstetricia et Gynecologica Scandinavica*, 96(8), 954-959. <https://doi.org/10.1111/aogs.13139>

Live birth outcome, spontaneous pregnancy and adoption up to five years after undergoing assisted reproductive technology treatment

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Key words

Adoption, assisted reproductive technology, follow up, infertility, longitudinal cohort study, spontaneous pregnancy

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Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Please cite this article as: Volgsten H, Schmidt L. Live birth outcome, spontaneous pregnancy and adoption up to five years after undergoing assisted reproductive technology treatment. *Acta Obstet Gynecol Scand* 2017; 96:954–959.

Received: 8 January 2017
Accepted: 28 March 2017

DOI: 10.1111/aogs.13139

Summary

Introduction. This study is part of a longitudinal cohort undertaken in both women and men to describe live birth outcome after undergoing assisted reproductive technology (ART) treatment in a clinical setting. Another objective was to follow women and men living with children from other alternatives after ART, such as adoption. **Material and methods.** A total of 439 (80.5%) women and 423 (77.6%) men were included in the baseline cohort (2005–2007). Live birth rate after ART was 24.8% at baseline. Up to 5 years later (2010–2011) the same participants were sent individual postal questionnaires ($n = 439$). **Results.** Overall, 278 (63.3%) women and 183 (41.7%) men filled in and returned the questionnaire at follow up. The majority of women (91.7%) and men (93.4%) were living with children. A total of 225 (80.9%) women had a live birth at follow up. Of these, almost three of four (71.6%) had a live birth after ART and more than one of four (28.0%) after spontaneous pregnancies or both. Of these, 52 (26.1%) women had a subsequent live birth after successful ART and 26 (32.9%) women after unsuccessful ART. Nineteen (6.8%) women and 13 (7.1%) men had a child after adoption. Almost one of five (19.1%) women had no live birth at follow up. **Conclusion.** The majority of women and men were living with children, resulting from a live birth after ART, spontaneous pregnancy and/or adoption up to 5 years later. However, almost one of five had no live birth at follow up.

Abbreviations: ART, assisted reproductive technology; MAR, medically assisted reproduction.

Introduction

In Sweden, assisted reproductive technology (ART) treatment is offered by both public and private clinics. About 14 400 ART treatments are performed annually, resulting in almost 4000 live births, or 4% of all children born, according to register data from a total of 16 fertility clinics, six public and 10 private. The live birth rate after one ART treatment is between 25 and 28% (1). About 500 children were the result of international adoption in 2015 according to Official Statistics of Sweden (2016).

Key Message

The majority of women and men were living with children up to 5 years after ART. Almost three of four women had a live birth after ART and one of four after spontaneous pregnancies or both. However, almost one of five women had no live birth at follow up.

However, to have a child after spontaneous pregnancies or adoption is not assessed in register data in couples undergoing ART treatment. Follow up of outcome after ended ART, such as spontaneous pregnancies and adoption, in clinical settings are few (2,3). Spontaneous pregnancies have been found among couples after ART and, depending on outcome after treatment, were successful or not. A retrospective cohort study found that 24% of couples with unsuccessful treatment had a spontaneous pregnancy. More than half of the spontaneous pregnancies occurred during the first 2 years after the last ART at the clinic (4). Another retrospective study after successful ART treatment showed that almost 21% had a subsequent spontaneous pregnancy after ART within 2 years and women with unexplained infertility were more likely to conceive (5). Furthermore, a retrospective study showed that 10 years after undergoing ART treatment, 82% of couples were living with children; 47% after ART, 15% after spontaneous pregnancies and 10–15% after other alternatives, such as fostering a child or adoption (6). Less is known about the decision to adopt after unsuccessful treatment and whether the decision depends on the outcome of treatment.

However, longitudinal cohort studies describing the outcome of treatment after ending ART in a clinical setting are few. Therefore, this follow up of outcome of treatment, such as live birth after ART or after spontaneous pregnancy up to 5 years after undergoing ART, was conducted. Another aim was to conclude whether women and men were living with children from adoption or other alternatives.

Material and methods

Study population

This is part of a longitudinal prospective study described elsewhere (7). All women and men in consecutive couples undergoing ART treatment at the Center of Reproduction, Uppsala University Hospital, Sweden, were invited to participate in 2005–2007. The Center of Reproduction is public and, at the time of the study, couples with no child in common were offered three subsidized ART treatments. For further treatments at the clinic the couples had to pay. The waiting list for ART was approximately 3 months. Pretreatment in clinics outside Uppsala County was done in approximately up to 40.0% of treatments and those women had their live birth outside the county. Overall, 862 (79.1%) participants were included and the baseline response rates were 439 (80.5%) for women and 423 (77.6%) for men. Almost three of four (74.3%) women had their first

ART; the live birth rate after ART was 24.8% in the baseline cohort. Between 4.5 and 5 years later (2010–2011), the same couples were sent follow-up questionnaires by mail to the home address of the woman ($n = 439$). All participants had previously consented to be contacted for this follow-up study. Socio-demographic and medical data were collected by asking the participants to fill in a postal questionnaire. Spontaneous pregnancies and adoption rates were assessed from the self-reported data in the questionnaire. The outcome of treatment, such as live birth after ART, was collected from the women's medical records by the first author (H.V.).

Study design

This study was conducted with individual questionnaires sent to the woman's home address. Women and men were asked for their consent to participate in the study and to complete and return the questionnaire by mail in the attached individual prepaid envelope. Two reminders were sent within 3 weeks.

Data collection

Socio-demographic and medical data were assessed in the postal questionnaire: for example age, weight, smoking, educational level, infertility duration, infertility factors and whether living with the same partner as at baseline. Other questions, such as numbers of ART, if ended or planning to continue ART, live birth after ART, spontaneous pregnancies and whether living with children from other alternatives, such as adoption or waiting for adoption and if living with child from previous or partners' previous relationship were also assessed. Comments could be given as for reasons not to adopt. Outcome of ART treatment, such as live birth, was collected from the women's medical records in the clinics database, for women participating or not in the study.

Statistical analyses

Continuous variables were presented as mean \pm SD. Frequencies were compared between groups using the chi-square test. All statistical analyses were performed with SPSS 22.0. A p -value less than 0.05 was considered significant. Multiple logistic regression analysis was used to calculate adjusted odds ratios (OR) and 95% confidence intervals (CI) for factors associated with outcome of treatment after ART, such as female age, duration of infertility and infertility factor.

The study was approved by the Ethics Committee, Uppsala University, Sweden (Dnr 2005:029).

Results

Study population

A total of 439 women and men respectively ($n = 878$) were eligible for the follow-up study. Of these, 461 (52.5%) agreed to participate and filled out and returned the questionnaire. Overall, the response rates were 278 (63.3%) for women and 183 (41.7%) for men. Where both partners responded, 181 (65.1%) women and men were matched as couples. Socio-demographic and medical data are given in Table 1 for women and men. Duration of infertility was $5.1 (\pm 3.1)$ years, and unexplained

infertility (42.8%) was the most prevalent infertility factor. The mean number of ART was $2.0 (\pm 1.0)$ and 21 (7.5%) women had more than three ART treatments at the public clinic. Of all women ($n = 278$); 217 (78.0%) women stated they had ended ART treatment, 42 (15.1%) were not sure and 19 (6.8%) wanted or planned to continue privately paid ART treatment. Most women (92.8%) and men (98.9%) were living with the same partner as during ART and had been in the same relationship for a mean of $12.2 (\pm 4.0)$ years. Twenty (7.2%) women were divorced. Among those not living with the same partner ($n = 20$), more women (35.0%) were living without a child than among women living with the same partner (6.2%) ($p < 0.05$).

Table 1. Socio-demographic and medical data of the study population at five-year follow-up.

	Women $n = 278$	Men $n = 183$
Age (year, mean \pm SD)	38.3 ± 3.9	39.7 ± 4.7
BMI, kg/m (mean \pm SD)	24.9 ± 4.5	
Smokers, n (%)	16 (5.8%)	6 (3.3%)
Duration of infertility (years, mean \pm SD)	$5.1 (\pm 3.1)$	$5.1 (\pm 3.04)$
Employed, n (%)	217 (78.0%)	170 (92.9%)
Student, n (%)	15 (5.4%)	1 (0.5%)
Parental leave, n (%)	28 (10.1%)	4 (2.2%)
Unemployed, n (%)	9 (3.3%)	3 (1.6%)
Sick leave, n (%)	7 (2.5%)	5 (2.7%)
Infertility factors		
Female, n (%)	66 (23.9%)	45 (24.7%)
Male, n (%)	55 (19.9%)	37 (20.3%)
Combined, n (%)	21 (7.6%)	15 (8.2%)
Unexplained, n (%)	118 (42.8%)	63 (34.6%)
"Don't know", n (%)	16 (5.8%)	21 (11.6%)
Number of treatments		
1 ART	107 (38.4%)	
2–3 ART	150 (53.9%)	
≥ 4 ART	21 (7.5%)	
Ended ART treatment	217 (78.0%)	150 (82.4)
Unsure/don't know	42 (15.1%)	19 (7.1)
Want/plan to continue ART	19 (6.8%)	13 (10.4)
Living with same partner	258 (92.8%)	181 (98.9)
Live birth at follow up	225 (80.9%)	
Child after treatment ^a		
After ART	199 (71.6%)	
Spontaneous	78 (28.0%)	
Living with children	255 (91.7%)	171 (93.4%)
Adoption	19 (6.8%)	13 (7.1%)
Planning/waiting to adopt	11 (3.9%)	12 (6.6%)
Child by other alternative	36 (12.9%)	21 (11.4%)
Child by previous relationship	8 (2.9%)	13 (7.1%)
Partner has child	24 (8.6%)	5 (2.7%)
Foster child	2 (0.7%)	2 (1.0%)
"Other"	2 (0.7%)	1 (0.5%)

^aSubjects can have children from more than one alternative. ART, assisted reproductive technology; BMI, body mass index.

Outcome of ART treatment

At the time of follow up, 225 (80.9%) women had a live birth and 53 (19.1%) women had not achieved a live birth. In all, 199 (71.6%) women had a child as a result of ART and 78 (28.0%) after spontaneous pregnancies or both (Table 1). Of women with spontaneous pregnancies, 52 (26.1%) women had a subsequent live birth after successful ART ($n = 199$) and 26 (32.9%) women after unsuccessful ART treatment ($n = 79$).

Living with children

Overall, most women (91.7%) and men (93.4%) were living with children at follow up. Thirty-six (12.9%) women and 21 (11.4%) men stated they were living with children from other alternatives; of these, 24 (8.6%) women and five men (2.7%) were living with a child from their partners' previous relationship. Nineteen (6.8%) women and 13 (7.1%) men had a child after adoption and 11 (3.9%) women and 12 (6.6%) men were waiting or planning for adoption (Table 1). In women adopting or waiting for adoption ($n = 30$), four (13.3%) women had a child after ART. Reasons not to adopt was added as comments in the questionnaire: by 76 (27.3%) women at follow up: 30 (39.4%) women stated that "me or my partner do not want to adopt", seven (9.2%) women that "I want but not my partner", and 38 (50%) women cited "other reasons". Economic reasons were only stated by one woman.

Analysis of participants and non-participants

Data were compared between women participating ($n = 278$) and not participating ($n = 161$) in the study. For women who declined to participate in the study, 48 (29.8%) had their pretreatment outside the county and were lost to follow up, three (1.8%), had emigrated or no data was found and two (1.2%) had divorced. A total of

108 women were left for follow up in the medical records. Of these, 77 (71.2%) women had a live birth after ART treatment. There was no difference found in live birth rate after ART in women participating and those not participating in the study (data not shown). For 31 (28.7%) women there was no live birth after ART at the time of follow up. For those women with unsuccessful ART treatment, there was no information about whether they were living with children from other alternatives such as partners' child or adoption.

Factors associated with outcome after ART

Female age ≤ 35 years and duration of infertility ≤ 5 years were significantly associated with a higher probability of achieving a live birth after ART ($n = 199$; $p < 0.05$). An unsuccessful ART treatment or no spontaneous pregnancy was significantly associated with a higher probability of adoption ($p < 0.05$; Tables 2 and 3). In women with spontaneous pregnancy ($n = 78$), duration of infertility ≤ 5 years and unsuccessful ART treatment were associated with live birth ($p < 0.05$; Table 3).

Discussion

This longitudinal prospective cohort study describes the outcome of treatment up to 5 years after undergoing ART in a clinical setting. The majority of the women and men were living with children; almost three of four

women had a live birth after ART and one of four had a spontaneous pregnancy. Of women with spontaneous pregnancies one of four had a subsequent live birth after a previous successful ART and almost one of three after unsuccessful treatment. About one of 10 women and men were living with children from other alternatives, such as partners' child, and less than one of 10 had a child after adoption at follow up. However, almost one in five women had no live birth at follow up.

This result is in accordance with a Danish longitudinal cohort study showing that 5 years after first inclusion in medically assisted reproduction (MAR), 69.4% of couples had a live birth (after treatment/no treatment) and 5.9% had a child after adoption (2). In contrast, a Swedish study showed lower rates up to 5.5 years after ART; in that study, 76.7% of the couples were living with children. This cohort was followed after unsuccessful ART: almost 40% had a biological child, 35% had adopted and almost 7% were living with their partner's child or a foster child at follow up (8), results in accordance with another follow up 6 years after unsuccessful treatment (9). For couples retrospectively followed 8 years after unsuccessful ART treatment, 71% of couples were living with children at follow up: 48% after live birth, 12% after spontaneous pregnancies and 11% after adoption (3). Furthermore, 20 years after treatment, almost 91% of

Table 2. Odds ratios (OR) (95% confidence intervals) for live birth after assisted reproductive technology (ART) treatment by female age, duration of infertility, infertility factor, and adoption.

	Live birth after ART Women, $n = 278$		Adjusted odds ratio	95% Confidence interval
	Yes = 199	No = 79		
Female age				
>35 years	146 (73.4)	69 (87.3)	ref	
≤ 35 years	53 (26.6)	10 (12.7)	0.36*	0.14–0.95
Duration of infertility				
>5 years	61 (31.6)	41 (60.3)	ref	
≤ 5 years	132 (68.4)	27 (39.7)	0.41*	0.21–0.78
Infertility factor				
Female/male factor	105 (52.8)	37 (48.1)	ref	
Unexplained factor	94 (47.2)	40 (51.9)	1.84	0.95–3.54
Adoption				
No	197 (99.5)	60 (76.9)	ref	
Yes	1 (0.5)	18 (23.1)	0.01*	0.00–0.13

ART, assisted reproductive technology.

* $p < 0.05$, missing items = 19.

Table 3. Odds ratios (95% confidence intervals) for live birth after spontaneous pregnancy by female age, duration of infertility, infertility factor and adoption.

	Spontaneous pregnancy Women $n = 278$		Adjusted odds ratio	95% Confidence interval
	Yes = 78	No = 200		
Female age				
>35 years	57 (73.1)	158 (79.0)	ref	
≤ 35 years	21 (26.9)	42 (21.0)	0.69	0.35–1.33
Duration of infertility				
>5 years	19 (25.3)	83 (44.6)	ref	
≤ 5 years	56 (74.7)	103 (55.4)	0.44*	0.23–0.86
Infertility factor				
Female/male factor	32 (41.6)	110 (55.3)	ref	
Unexplained factor	45 (58.4)	89 (44.7)	0.62	0.35–1.11
Adoption				
No	77 (100)	180 (90.5)	ref*	–
Yes	0 (0)	19 (9.5)	0.00	
Previous live birth after ART				
Yes	52 (66.7)	147 (73.5)	ref	
No	26 (33.3)	53 (26.5)	0.37*	0.18–0.74

* $p < 0.05$, missing items = 19.

couples were living with children, biological (58%) or adopted (21%) or both (10). The results for spontaneous pregnancies in this study are somewhat higher than in a French study where 17% of couples with successful ART and 24% with unsuccessful ART had a spontaneous pregnancy within the first 4 years of treatment (4).

More women in the current study had a spontaneous pregnancy after ART in contrast to the study by Pinborg *et al.* (2) where 18% conceived spontaneously; up to 7 years after, spontaneous pregnancies occurred in 28% of all couples (11). However, an Australian follow up within 2 years showed a higher prevalence of spontaneous pregnancies after both successful (33%) and unsuccessful (40%) ART treatment (12). A factor associated with both spontaneous pregnancies and successful ART in the current study was short duration of infertility. An unexplained infertility factor was the most prevalent factor in this cohort. Both factors are common in an infertility cohort and influence the live birth outcome. More spontaneous pregnancies are suggested to follow when the factor is unexplained (4,11) and expectant management is recommended (2). Therefore, women with unexplained infertility may wait longer than women with explained infertility, at least at clinics as in this study where there is a short waiting list for ART treatment. However, in a small retrospective cohort study with a spontaneous live birth of 22% after successful ART, the authors concluded that the rate of spontaneous pregnancy remained unchanged regardless of the number of treatment and are not associated with being referred to ART too early (13). Therefore, short duration of infertility is not a factor, such as unexplained infertility, where expectant management can be suggested.

Most couples in the current study were living with the same partner as during treatment in accordance with another study where the rate was 92.9% of couples living together (2). This result was in agreement with a 20-year follow up after treatment in which the majority stated they were still in the same relationship as during ART (10). Hence, divorce is not a factor associated with undergoing ART, in particular when outcome of treatment has been successful. On the other hand, among women in this study not living with the same partner, more women were living without a child than with the same partner.

The majority of the women and men were living with a biological child at follow up. An unsuccessful outcome of ART was associated with adoption. Almost one in five women had no live birth after ART and half of these had adopted or were waiting or planning for adoption at follow up. Surprisingly, half of the women responding to the questionnaire mentioned "other reasons" for not wanting or planning to adopt. Those reasons were not

revealed and further studies of what is affecting couples' decision-making to adopt are needed. About one-fifth of couples in another study stated they wanted to pursue adoption after 1 year of unsuccessful treatment (14). However, these couples had not ended MAR treatment. At a five-year follow up of the same couples, only 6% had pursued adoption (2), in accordance with this study. More than three of four women in the current study indicated they had ended ART treatment. Adoption is suggested to be considered when other options no longer are feasible (15). Couples applying for adoption have to overcome their grief at not having a biological child (16). Furthermore, adoption is a long-term procedure and, in Sweden as in Denmark, ART treatment has to be ended before the adoption process can start (17).

A clinical implication of this result is to counsel couples prior to treatment that the chance of live birth after ART is almost three out of four up to 5 years after ART and, furthermore, that spontaneous pregnancies occur after both successful and unsuccessful ART. However, one in five women in the current study had an unsuccessful outcome after undergoing ART treatment at follow up, a number consistent with other studies (8); for those couples with no live birth after treatment, information about other alternatives needs to be provided concerning living with children, such as adoption.

One strength of the present study was the longitudinal prospective design in a clinical setting assessing the outcome after treatment in the same cohort. Other studies have a cross-sectional design, as for couples with adoption (15,16). In the current study, couples with both successful and unsuccessful outcomes after ART were included at follow up. Thus, this study is one of few following the same couples in the same clinical setting and describing their continuation with adoption after undergoing unsuccessful ART. Other strengths were the possibility to obtain data on live birth outcome after ART in most couples, both those included and those not included in the study. The medical records showed no difference in live birth rate after ART in couples who participated and couples who declined to participate in the study.

A limitation of the study was that information was limited for those declining to participate who had an unsuccessful treatment, and whether they were living with children after adoption or other alternatives. Furthermore, there was no information about those couples not participating in the study living outside the county. However, lower response rates after unsuccessful treatment have been seen in other studies (3,6,8–10). Consequently, couples responding to follow-up questionnaires are more likely to have had successful ART treatments (18). Therefore, there can be a selection bias and the rate of spontaneous pregnancies can be overestimated among women

with unsuccessful ART and the adoption rate underestimated in this study.

In conclusion, up to 5 years after ART, the majority of the women and men were living with children; almost three of four women had had a live birth after ART treatment and one of four after spontaneous pregnancies or both. About one of 10 women and men were living with children from other alternatives, such as their partners' child and fewer than one of 10 had a child after adoption. However, for almost one of five women there was no live birth at follow up. For those couples, with no live birth after undergoing ART, information is needed about other alternatives, such as adoption.

Acknowledgments

We are grateful to the midwives Linn Hilding and Anette Nilsson Övringe for their invaluable help in distributing the postal questionnaires and collecting the data.

Funding

This study was supported by research grants from the Family Planning Foundation and the Foundation of Caring Sciences, Uppsala University, Sweden.

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